CORRESPONDENCE

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Imbalance of Neutrophils and Lymphocyte Counts Can Be Predictive of Hepatocellular Carcinoma Occurrence in Hepatitis C-related Cirrhosis Treated With Direct-acting Antivirals

Dear Editors:

We read with interest the article published by Debes et al.[1] These investigators observed that, in patients with hepatitis C-related cirrhosis, the serum levels of inflammatory cytokines before treatment and their modification with direct-acting antiviral (DAA) were associated with occurrence or recurrence of hepatocellular carcinoma (HCC). An additional hypothesis may be a dysregulation of the antitumor response after the sharp decrease in the hepatitis C viral load induced by DAA therapy, promoting tumor development. We evaluated whether changes in neutrophil and lymphocyte counts during treatment with DAA can be associated with HCC development. Retrospective laboratory data obtained at baseline and at the end of treatment in 308 consecutive patients with hepatitis C-related cirrhosis, but without previous HCC, were evaluated. Patients were treated with different approved DAA regimens at different centers in the metropolitan area of Bologna, Italy, between March 2015 and August 2016. After a median follow-up of 10.5 months from the end of treatment, HCC was detected and confirmed by $\geq$2 independent imaging techniques or biopsy in 23 of 308 patients (7.24%). A significant increase in neutrophil counts (2.88×10^9/L $\pm$ 1.21 vs 3.32×10^9/L $\pm$ 1.32; $P = .0002$) and a significant decrease in lymphocyte counts (1.61×10^9/L $\pm$ 0.84 vs 1.46×10^9/L $\pm$ 0.79; $P = .037$) were observed between baseline and the end of treatment. We evaluated the difference in neutrophils and lymphocytes between baseline and the end of treatment in patients with or without HCC occurrence. In patients with HCC development (n = 23), we observed a significant increase in neutrophils (2.35×10^9/L $\pm$ 1.02 vs 3.11×10^9/L $\pm$ 1.26; $P = .033$) and decrease in lymphocytes (1.78×10^9/L $\pm$ 1.07 vs 0.99×10^9/L $\pm$ 0.53; $P = .003$) during treatment. In patients without HCC development (n = 285), there was a similar trend, but it was not statistically significant (neutrophils: 3.00×10^9/L $\pm$ 1.26 vs 3.23×10^9/L $\pm$ 1.41 [$P = .08$]; lymphocytes: 1.66×10^9/L $\pm$ 0.86 vs 1.54×10^9/L $\pm$ 0.85 [$P = .14$]).

It is well-known that neutrophils promote adhesion and seeding of distant organ sites through the secretion of circulating growth factors such as vascular endothelial growth factor and proteases.[2,3] In contrast, cytotoxic T lymphocytes play a crucial role in tumor defense inducing tumor cell death and inhibiting tumor cell proliferation and migration, thereby dictating the host's immune response to malignancy.[2] Our study suggests that, during DAA treatment, there is a significant imbalance between lymphocytes and neutrophils that is particularly evident in subjects developing HCC. This imbalance may result in an unfavorable microenvironment that favors the growth of cancer cells. Thus, inflammation may induce changes in the cancer microenvironment favoring cancer progression.[2] Based on these observations, we suppose that treatment with DAA, in some patients, can induce the deregulation of immune defenses characterized by an increase of vascular endothelial growth factor, leading to an early development of HCC, as suggested by Debes et al[1] and by Villani et al[5] in a recently published study.

In this complex context, evaluation of changes in neutrophil and lymphocyte counts during treatment with DAAs adds a simple and easily to obtain information about the patient's inflammatory state and their possible risk of developing HCC after DAA treatment. Q4

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Conflicts of interest
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